

## REMARKS / ARGUMENTS

Claims 1-55 are pending in the application. Claims 1, 17, 28, 37, 44 and 45 have been amended without prejudice or disclaimer of any previously disclaimed subject matter. Applicants respectfully request entry of the amendments submitted herewith.

### ***Objection to the Specification***

The Examiner has noted that the specification has not been checked to the extent necessary to determine the presence of all possible minor errors and requests Applicants cooperation in correcting any errors of which Applicants may become aware. Applicants agree to submit amendments to correct any errors in the specification of which they become aware, and do not have any amendments to the specifications at this time.

### ***Rejection under 35 U.S.C. § 112***

The Examiner has rejected claims 17, 28, 37 and 44 under 35 U.S.C. 112, second paragraph, as indefinite. The Examiner asserts that the limitation recited in claims 17, 28, 37 and 44 of "acetic anhydride substituted by a protected or unprotected amino" is unclear. Claims 17, 28, 37 and 44 have been amended, without prejudice or disclaimer, to remove the phrase "or unprotected". Applicants submit that amended claims 17, 28, 37 and 44 are definite and respectfully request withdrawal of this rejection.

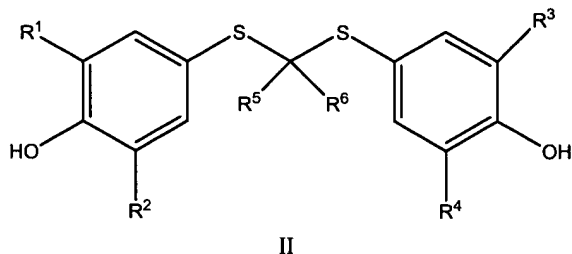
### ***Rejections under 35 U.S.C. § 103***

The Examiner has rejected claims 1-15, 17-26, 28-37, and 45-55 35 U.S.C. § 103(a) as obvious over Medford et al. (WO 98/51662) in view of U.S. Patent No. 6,806,381 (Chidambaram et al.) and Aldrich (Aldrich Chemical Catalog, 2002, Milwaukee, WI, pages 187, 1104, 1454, and 1597.)

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. The prior art must provide motivation to one of ordinary skill in the art to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987); *in re Lalu and Foulletier*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie*

obvious if the primary references do not suggest all of the elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 USPQ2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989).

Amended claim 1 of the present application recites a process of manufacturing a compound of Formula I or salts thereof comprising: 1) reacting a compound of Formula II

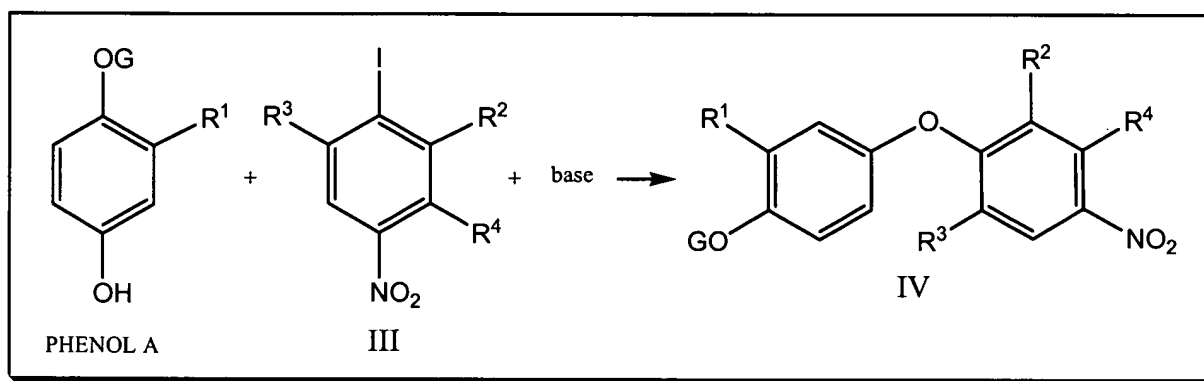


with a Grignard Reagent to form a magnesium salt or a reagent selected from the group consisting of an alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl lithium, and a heteroaryl lithium, all which can be optionally substituted to form a lithium salt; 2) reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated acyl halide, saturated or unsaturated carboxylic acid anhydride and a saturated or unsaturated activated carboxylic acid ester, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, amino, halo, protected carboxy and cyano; 3) separating and isolating said compound of Formula I.

Similarly, amended claim 45 recites a process of manufacturing a compound of Formula I or salts thereof comprising: 1) reacting a compound of Formula II with a Grignard Reagent to form a magnesium salt or a reagent selected from the group consisting of an alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl lithium, and a heteroaryl lithium, all which can be optionally substituted to form a lithium salt; 2) reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano; 3) separating and isolating said compound of Formula I or salts thereof.

The Examiner has stated that Medford et al. teaches methods for the mono O-alkylation and O-acylation of probucol via formation of sodium phenolate by treatment with sodium hydride. The Examiner further notes that Medford et al. does not appear to contemplate the use of Grignard reagents or alkyl lithium reagents as bases instead of sodium hydride. Applicants agree that Medford et al. does not disclose or suggest the substitution of Grignard reagents or alkyl lithium reagents for sodium hydride in the preparation of monoethers and monoesters of probucol.

The Examiner states that Chidambaram et al. teaches a method for the deprotonation of phenols by treatment with base and "for the purpose of deprotonating phenols that alkali metal hydrides, alkyl lithium reagents and Grignard reagents are equivalent". Applicants note that the reaction of Chidambaram et al. described on column 13, lines 42-56, which the Examiner refers to is the following:



and the cited passage in Chidambaram et al. states:

The coupling reaction to form the mixed ether of formula IV from the compound of formula III and phenol A is conducted in the presence of a base. Preferred bases include, e.g., alkyl lithiums, lithium diisopropylamine, Grignard reagents, alkali metal hydrides, alkali metal carbonates, alkali metal hydroxides, and alkali metal alkoxides. ... More preferably, the coupling reaction is performed in toluene/DMF or toluene/THF or DMF at room temperature using potassium hexamethyldisilazide (KHMDs), potassium t-butoxide, potassium t-pentoxide, LiHMDS, or NaHMDS as the base.

As shown above, the coupling reactions described in Chidambaram et al. are limited to certain 3,4-substituted phenol compounds. Contrary to the Examiner's assertion, one of ordinary

skill in the art would not be motivated by the chemistry described in Chidambaram to apply its teaching to the probucol-like starting materials of the present invention.

Applicants submit U.S. Patent No. 6,323,359 ("the '359 patent") to Salsbury Chemicals, Inc. The '359 patent describes processes of preparing certain probucol-like compounds from probucol. The data provided in the table in the '359 patent (columns 5-6 of the '359 patent, reproduced below) provides a comparison of several bases and the influence of each on the resulting ratio of products of the reaction.

TABLE

Example	Base (mol. equivalent)	DSP	MSP	Probucol	Reaction Time (hrs)	Temp ° C.
2	KOtBu(2.21)	15.10	48.66	36.19	2.0	Ambient
3	DMAP(2.18)	0	0.14	98.65	2.0	29
		0	1.17	96.82	18.0	30
4	KOtBu(2.10)	13.20	46.48	40.33	2.0	30
5	DABCO(2.21)	0.59	12.23	87.18	3.0	60
6*	KOtBu(2.10)	6.68	37.78	55.37	2.0	30
		8.51	37.73	55.76	78.5	60
7	KOtBu(1.00)	4.11	29.97	66.32	2.0	30
8	KOtBu(5.10)	12.13	45.34	42.11	1.9	30
9	KOH(2.20)	0.30	10.60	88.80	2.0	Ambient
10	KOtBu(2.20)	22.60	25.50	72.00	2.0	Ambient
	ALIQUAT ®336 (2.20)					
11	KOH(2.2)	5.50	33.40	61.2	2.0	Ambient
	TEA Cl(2.2)					
comparative	KOtBu(0.10)	0	0	100.00	2.0	30

\*acrylonitrile, 150 mL was used in place of THF

Note: In Examples 10 and 11, a reaction between the two components shown in the column "Base (mol. equivalent)" precipitates potassium chloride, generating the respective alkylammonium alkoxide or alkylammonium hydroxide in situ.

The Examiner's attention is directed to the results of Examples 2 and 9 in the table above. Example 2 describes a reaction which involves potassium tert-butoxide (an "alkali metal alkoxide") as the base and produces 48.66 mol % monosuccinylated probucol and 15.10 mol % disuccinylated probucol. In contrast, Example 9 describes a reaction which involves potassium hydroxide (an "alkali metal hydroxide") as the base and produces 10.60 mol % monosuccinylated probucol and 0.30 mol % disuccinylated probucol. Both reactions occur over two hours at ambient temperature in tetrahydrofuran (THF). This data clearly demonstrates that

alkali metal alkoxides and alkali metal hydroxides **are not** equivalent when used to deprotonate probucol.

The Examiner states that Chidambaram et al. teaches, for the purpose of deprotonating phenols that alkali metal hydrides, alkyllithiums and Grignard reagents are equivalent and asserts that therefore one of ordinary skill would be motivated to use such reagents in the claimed process. Included in the Chidambaram list of bases are both alkali metal alkoxides and alkali metal hydroxides. As discuss above, it was known *prior to the publication of Chidambaram et al.* that these bases are ***not*** equivalent for probucol. Based on this evidence, one of ordinary skill in the art reading Chidambaram et al. would recognize that the chemistry and the “preferred” bases discussed in Chidambaram could not be broadly interpreted and would specifically recognize that the listed bases are not equivalent for the chemistry of probucol.

The Examiner has used Aldrich in combination with Chidambaram asserting that Aldrich (Aldrich Chemical Catalog, 2002, Milwaukee, WI, pages 187, 1104, 1454, and 1597) teaches the specific Grignard and lithium reagents used in the Examples of the present application. The Aldrich Chemical Catalog merely provides a listing of their compounds which are available for purchase. It *does not* advise on the equivalency or potential substitutions of any of these compounds.

No combination of Medford et al., Chidambaram et al. and/or the Aldrich Chemical Catalog would suggest all the limitations of the claims to one of ordinary skill in the art. Therefore, Applicants respectfully request the withdrawal of this rejection.

### **Claims Objections and Allowable Subject Matter**

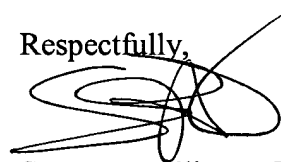
The Examiner has objected to claims 16, 27 and 38-44 as dependent upon a rejected base claim. The Examiner has also indicated that claims 16, 27 and 38-44 would be allowable if rewritten in independent form including all of the limitations of the base claim. Applicants thank the Examiner for this indication of allowable subject matter.

**Conclusion**

In view of the amendments and arguments presented herein, Applicants respectfully request that the Examiner withdraw the outstanding rejections in this matter, and that this application be returned to the Examiner with instructions to enter a notice of allowance.

The Commissioner is authorized to charge any fee associated with this Amendment, as well as any other deficiency, or credit any overpayment, to Deposit Account 11-0980.

Respectfully,

A handwritten signature in black ink, appearing to be 'Susanne Hollinger', written over a horizontal line.

Susanne Hollinger, Ph.D.  
Reg. No. 51,811

King & Spalding  
1180 Peachtree Street NE  
Atlanta, Georgia 30309-3521  
404-572-2485 (Direct Line)  
404-572-5134 (Facsimile)